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LES SÉMINAIRES DE L'INMG

*Cancer and Cancer treatments on
cognition: A major translational impact
of the preclinical research*

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ABSTRACT :

Co-head Cancer and Neurosciences axis Northwest canceropole, Cancer and cognition platform; ICCTF member (editing of preclinical research guidelines).

The emergence of a new field in oncology addressing cognitive deficits in cancer patients is justified by the existence of deficits in memory, concentration and attention, as well as executive functions before, during and after treatments, symptoms often referring to the “chemofog” or “cancerfog”. Our work mainly involves research and clinical groups of Normandie developing programs in patients and animal models, to improve our understanding of the impact of cancer and its treatments on cognitive functions. Two main examples of these translational studies we participated on can be exposed:

The first Cog-Age clinical study (Pr F. Joly, Baclesse Caen) showed that cognitive decline can be detected 6 months after chemotherapy in breast cancer elderly patients². In a mirror study, chemotherapy administration in young and elderly mice resulted in a change in behavioral flexibility and alteration of neuron precursor proliferation in the hippocampal dentate gyrus. We were thus able to conclude that age-related cognitive decline is accentuated by chemotherapy, providing basis for questioning the place of adjuvant chemotherapy in this elderly patient population. The second clinical study COG-ANGIO (Pr Joly) demonstrated that antiangiogenics exert a direct negative impact on cognitive functions and fatigue in kidney cancer patients⁴. In mice, the anti-angiogenic mTOR inhibitor everolimus did not alter cognitive functions but led to weight loss and modification of cell metabolism in brain regions involved in sleep/wake cycle or food intake, likely connected to fatigue⁵. On the other hand, immunoneutralizing VEGF (Genentech-Roche, MTA) impaired spatial learning performance and neuronal activity of CA3 hippocampus neurons. These data suggest that a careful and systematic evaluation of targeted cancer therapies on cognitive functions in preclinical models may constitute a strategy of prevention by selection of treatments exhibiting minimum brain co-morbidities.

Together, this translational program is developed within the National Cancer and Cognition Platform (CNO/Ligue Nationale contre le cancer), with the aim to collaborate in a structured way with French oncology groups, research teams as well as pharmaceutical industry, by providing preclinical models and guidance on standard operating procedures for ancillary or future studies in identified population at risk⁶.

RECENT PUBLICATIONS :

1. Joly F, Giffard B, Rigal O, De Ruyter MB, Small BJ, Dubois M, LeFel J, Schagen SB, Ahles TA, Wefel JS, Vardy JL, PancrÃ© V, Lange M, **Castel H**. Impact of Cancer and Its Treatments on Cognitive Function: Advances in Research From the Paris International Cognition and Cancer Task Force Symposium and Update Since 2012. *J Pain Symptom Manage*. 2015 Dec;50(6):830-41.
2. Lange M, Heutte N, Rigal O, Noal S, Kurtz JE, LÃ©vy C, Allouache D, Rieux C, Lefel J, Clarisse B, Veyret C, BarthÃ©lÃ©my P, Longato N, **Castel H**, Eustache F, Giffard B, Joly F. Decline in Cognitive Function in Older Adults With Early-Stage Breast Cancer After Adjuvant Treatment. *Oncologist*. 2016 Jul 29.
3. Dubois M, Lapinte N, Villier V, Lecointre C, Roy V, Tonon MC, Gandolfo P, Joly F, Hilber P, **Castel H**. Chemotherapy-induced long-term alteration of executive functions and hippocampal cell proliferation: role of glucose as adjuvant. *Neuropharmacology*. 2014 Apr;79:234-48.
4. Joly F, Heutte N, Duclos B, Noal S, LÃ©ger I, Dauchy S, Longato N, Desrues L, Lange M, Sevin E, Rieux C, Clarisse B, **Castel H** and Escudier B. Prospective evaluation of the impact of antiangiogenic treatment on fatigue and cognitive functions in metastatic renal cancer. *European Urology Focus*, 2016, doi.org/10.1016/j.euf.2016.04.009.
5. Dubois M, Le Joncour V, Tonon MC, Anouar Y, Proust F, Morin F, Gandolfo P, Joly F, Hilber P, **Castel H**. Evaluation of the impact of the cancer therapy everolimus on the central nervous system in mice. *PLoS One*. 2014 Dec 1;9(12):e113533.
6. **Castel H**, Denouel A, Lange M, Tonon MC, Dubois M, Joly F. Biomarkers Associated with Cognitive Impairment in Treated Cancer Patients: Potential Predisposition and Risk Factors. *Front Pharmacol*. 2017 Mar 21;8:138.